years ago, first clinical trials on safety and immunogenicity. In the meantime more than 25,000 women have been included into several efficacy trials which demonstrated protection against persistent infection with HPV 16 and 18 and against the development of precursor lesions to cervical cancer. Although the ultimate proof of success, i.e. reduction of cancer incidence still requires the immunization of large populations and many years of follow-up, the existing data are so persuasive that the first marketing of the vaccine is expected to be announced in mid 2006. Yet several questions such as the duration of protection, the need development of for post-exposure vaccination strategies and availability of such vaccine in low-budget countries are open and will be discussed.

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S39. IDENTIFICATION OF POTENTIAL TARGET ANTIGENS FOR IMMUNOTHERAPY APPROACHES

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Immunotherapy approaches in cancer rely on the identification of suitable antigens that can be used as targets for therapeutic approaches. The ideal target antigen is highly and homogenously expressed in cancer, but not or low level expressed in normal tissues. Using different cloning techniques, several potential target antigens have been identified, some of these antigens are already being evaluated in clinical trials. We followed a cloning strategy called SEREX that identifies tumor antigens based on a spontaneous humoral immune response in patients. Using this technique we identified 2 new tumor associated antigens that belong to the group of differentiation antigens: NY-BR-1 as a new breast differentiation antigen and RAB38/NY-MEL-1 as a new melanocyte differentiation antigen.

NY-BR-1 is not expressed in normal tissues except in normal mammary gland and testis, but it is highly expressed in 70% of breast cancers. Antigen positive cancers maintain the expression in metastatic lesions. Spontaneous antibody responses occur in about 10% of breast cancer patients. We identified 2 HLA-A2 restricted NY-BR-1 derived epitopes that were recognized by CD8+ T cells from patients with NY-BR-1 expressing cancers. Both epitopes are naturally processed and presented.

RAB38/NY-MEL-1 is expressed in melanocytes and at low level in adrenal gland, all other normal tissues are RAB38/NY-MEL-1 mRNA negative. Spontaneous humoral immune responses are frequent in melanoma patients but not in normal individuals, in patients with vitiligo or with cancers other than melanoma. We recently identified a HLA-A2 restricted RAB38/NY-MEL-1 derived epitope that is naturally processed and presented and recognized by CD8 T cells.

Both new antigens, NY-BR-1 and RAB38/NY-MEL-1 are being evaluated as targets for T cell based immunotherapy strategies in Phase-I trials.

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S40. T CELL BASED IMMUNOTHERAPY – CHANGES AND CHALLENGES

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Advances in cellular and molecular immunology have led to the development of strategies for effective augmentation of anti-tumor immune-responses in cancer patients. This presentation focuses on the manipulation of T cell immunity either by active-specific immunization with tumor vaccines[1–4] or by adoptive immunotherapy with immune T cells.[5,6] Such therapies offer exquisite specificity of tumor recognition based on the ability of the T cell to distinguish single amino acid differences in any protein from any compartment of the tumor cell.

Recent analyses of bone marrow samples from patients with a variety of different cancers revealed the existence of cancer reactive memory T cells in a high proportion and at high frequencies.[5–9] A fine specificity analysis revealed *individuality* (i) of response patterns to multiple tumor associated antigens (TAAs), (ii) of the size and (iii) of the specificity of the memory repertoire in the bone marrow of cancer patients. These findings challenge immunotherapy approaches targeting single TAAs. Future strategies will be discussed for the exploitation of the TAA memory repertoire of cancer patients. In “proof of principle” studies it was demonstrated to have great therapeutic potential.[5,6]

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S41. TARGETING THE APOPTOTIC PATHWAY TO INDUCE RADIORESISTANCE IN NORMAL TISSUE AND STEM CELLS

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Novel strategies in clinical radiotherapy have the goal to increase the therapeutic index i.e. effective tumor cell kill while sparing the normal tissue. This can be achieved by either physical selectivity when the tumor is well circumscribed or by biological selectivity when normal tissue is present in the treatment volume. Biological selectivity can be achieved by targeting tissue properties which are only present either in tumor or normal tissue cells.

Radiation induced apoptosis is a rare event as compared to mitogenic death in epithelial tumor cells. In contrast, radiation

induced apoptosis for example of endothelial cells or bone marrow stem cells is clinically relevant as initiating step for normal tissue damage after radiotherapy.

We have established several gene-therapeutic approaches to suppress radiation induced apoptosis by overexpression of super-oxide dismutase (SOD) and P-glycoprotein (P-gp) the product of the multi-drug resistance gene (MDR). Clonogenic assays showed that radioresistance can be induced in normal tissue cells (e.g. human primary lung fibroblasts), whereas the survival of human tumor cells (e.g. HeLa) after radiotherapy is not altered. Using differential gene expression analysis and quantitative real-time PCR, we showed up-regulation of detoxification genes and down-regulation of pro-apoptotic genes (e.g. CASP1, CASP4).

Targeting the apoptotic pathway to induce radioresistance in normal tissue cells is a potential strategy to increase the therapeutic index in radiation oncology.

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S42. CHALLENGES IN DEFINING GENETIC RISKS FOR FAMILIAL COLORECTAL CANCER

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Twenty to twenty-five percent of all cases of colorectal cancer (CRC) show some familiarity. Although the role of genes is not yet completely understood, a number of well-defined genetic disease entities is known to contribute to the familiarity: Lynch syndrome (formerly hereditary nonpolyposis colorectal cancer, HNPCC), familial adenomatous polyposis (FAP), MYH-associated polyposis (MAP), juvenile polyposis, Peutz–Jeghers syndrome. The most common genetic form of CRC is Lynch syndrome that is responsible for 2–3% of all cases. The analysis of these diseases led to valuable insights into the disease process also of the sporadic forms of CRC.

We need a filter system within the public health care system that allows the detection of families with an increased genetic risk. Individuals belonging to such families should first undergo genetic counselling. Genetic analysis can largely differentiate between the risks. Persons at increased risk should be included in a risk-adapted screening programme. Only specialized centers for inherited CRC will be able to efficiently organize programs of CRC prevention.

The ongoing collaborative study of the German Cancer Aid will give clear data as to the efficacy of systematic cancer prevention in Lynch syndrome through early detection, particularly through colonoscopy and gynecological examinations.

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S43. MOLECULAR DIAGNOSIS OF HEREDITARY COLORECTAL CANCERS

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Hereditary colorectal cancer accounts for up to 5% of all colorectal cancers. A variety of known and unknown genes are responsible for the two known phenotypes. Familial adenomatous polyposis coli (FAP) is phenotypically characterized by hundreds or even thousands of polyps in the colon and rectum and by a very high incidence of colorectal cancer at young age. FAP is caused by the tumour suppressor gene *APC* and is a highly penetrant autosomal condition, while the phenotypically similar *MUTYH*-associated polyposis is an autosomal recessive disease.

The much more frequent hereditary non-polyposis colorectal cancer syndrome (HNPCC) is caused by mutations in five mismatch repair (MMR) genes. Although no clear-cut genotype/phenotype correlations in pathogenic mutations carriers of the same MMR gene have been identified, distinct phenotypic differences are associated with mutations in different MMR genes. The mode of inheritance of HNPCC is autosomal dominant, yet a small but increasing number of very young patients have been reported as carriers of biallelic MMR gene mutations. Notably, their phenotype is different from the HNPCC phenotype and resembles the phenotype of MMR gene knockout mice. In addition to an incomplete penetrance of about 80% for colorectal cancers, and susceptibility to a wide range of tumours, the age of onset of HNPCC varies widely, ranging from 16 to 90 years. We have identified additional genetic factors located in *p53* and *RNASEL* that influence age of disease onset in HNPCC patients carrying a pathogenic MMR germline mutation.

In conclusion, mutations in a variety of genes can cause hereditary colorectal cancer. In addition to genetic heterogeneity, there is evidence for multiple genetic factors that contribute to the development of disease. Identification of causative genetic and environmental factors may contribute to a more detailed tumour risk assessment in carriers of mutations in MMR genes. Particularly, the knowledge of the age of onset of disease in carriers of pathogenic germline mutations in MMR genes might affect preventive strategies, including age at first surveillance, surveillance intervals, and age at preventive surgery.

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S44. EGFR-SIGNALLING IN COLON CANCER

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Activation of the epidermal growth factor receptor (EGFR) pathway seems to be involved in the regulation of proliferation and invasion in gastrointestinal tumors. In colon cancer increased EGFR levels were reported in advanced and more invasive carcinomas. Recently EGFR-inhibitors are used as a new treatment option in patients not responding to standard chemotherapy. However, EGFR-signalling is dependent on the presence of various EGFR ligands and mechanisms of ligand presentation. In addition several other mechanisms involved in the regulation of EGFR binding have been reported (PKC, Syk, Mig6, SIRPs). Furthermore costimulatory effects between other G-protein coupled receptor (GPCR) were shown to increase tumor cell proliferation.